

REMARKS

Supplemental Information Disclosure Statement filed June 2003 with Previous Response

In the Supplemental IDS and accompanying Form PTO-1449 submitted by Applicants with the June 2003 Response, Applicants cited a reference (WO 01/66736), a copy of which had previously been submitted with the March 2003 IDS. The Office Action of November 2003 states that the citation of this reference was crossed out on the Form PTO-1449, and would not be considered because "the Examiner does not read Japanese, thus in order to consider the WO 01/66736, it has to be translated to English" (Office Action, page 2, item 3). For the reasons submitted below, Applicants respectfully request that the reference be considered and made of record.

Section 609 of the MPEP, particularly at section 609 III A(2) and section 609 III A(3) on page 600-122, describes the procedure for consideration of references submitted by Applicants that are not in the English language. Applicants are not required to submit a translation of a non-English language reference unless they have such a translation:

Translations are not required to be filed unless they have been reduced to writing and are actually translations of what is contained in the non-English language information. If no translation is submitted, the examiner will consider the information in view of the concise explanation and insofar as it is understood on its face, e.g., drawings, chemical formulas, English language abstracts, in the same manner that non-English language information in Office search files is considered by examiners in conducting searches. (MPEP, section 609 III A(2))

In the June 2003 Response, it was indicated that Applicants have not had a translation made of WO 01/66736, therefore Applicants are not required to submit a translation of this reference in order to have the reference made of record and considered by the Examiner (see 37 CFR 1.98(a)(3)(ii)).

Applicants have submitted a copy of the WO 01/66736 reference with the March 2002 IDS; they have properly cited the WO 01/66736 reference on the Form PTO-1449 submitted with the June 2003 Response; and they have provided a concise explanation of the relevance of the non-English language information contained in the WO 01/66736 reference (see 37 CFR 1.98(a)(3)(i)). In the Supplemental IDS submitted with the June 2003 Response, Applicants provided a concise explanation of the relevance of the WO 01/66736 reference by stating that the WO 01/66736 reference was submitted because it discloses murine nectin-3

polypeptides. In addition, in the June 2003 Response, Applicants respectfully directed the Examiner's attention to the EP 1179592 A and US 2003/0008334 A1 references as "publications in the English language of the European and US applications, respectively, corresponding to the WO 01/66736 PCT publication ... [t]hese publications (EP 1 179 592 A and US 2003/0008334 A1) each appear to be a translation of the WO 01/66736 publication into English". According to the MPEP, providing the corresponding EP or US English-language publications of non-English applications is another way to provide the concise explanation of 37 CFR 1.98(a)(3)(i):

A (3) Concise Explanation of Relevance for Non-English Language Information

... An English-language equivalent application may be submitted to fulfill this requirement if it is, in fact, a translation of a foreign language application being listed in an information disclosure statement. There is no requirement for the translation to be verified. (MPEP, section 609 III A(3))

Therefore, Applicants have complied with all of the requirements of 37 CFR 1.98 for submission of the WO 01/66736 reference, and consideration of this reference by the Examiner is respectfully requested. For the convenience of the Examiner, Applicants submit herewith a clean copy of the Form PTO-1449 submitted with the June 2003 Response.

Amendments to the Specification

In the June 2003 Response, Applicants submitted amendments to the paragraph beginning at page 6, line 15 and to Table 2 which begins at page 7, line 7. The October 2003 Office Action objected to these amendments on the basis that they introduced new matter; although Applicants do not accede to the basis for the objection, Applicants have in the present amendments submitted a replacement paragraph and Table. The present amendments do not include new matter.

With respect to the paragraph beginning at page 6, line 15, the present amendment restores this paragraph to its text as originally filed.

Table 2 as originally filed in the specification had a consensus sequence that included both capitalized letters and lower-case letters. The paragraph at page 6, line 15 indicates that the capitalized letters are consensus residues that are identical among at least a majority of the amino acid sequences in the alignment. The text of the specification does not describe the lower-case letters of the Table 2 consensus sequence in particularity, and their presence in the Table 2 consensus sequence may make it more difficult to read: for example, a lower-case 'v'

might easily be mistaken for a capital 'V'. The present amendment clarifies Table 2 by removing the lower-case letters from the consensus sequence; removing these characters does not introduce new matter. In addition, the present amendment to Table 2 corrects typographical errors so that the capitalized letters in the consensus sequence are consistent with the description of these capitalized letters in the paragraph at page 6, line 15: capital letters are now included in the Table 2 consensus sequence at every position where three or more of the five amino acid sequences in the alignment share amino acid identity. This correction of typographical errors in the Table 2 consensus sequence does not introduce new matter, and clarifies the presentation of the information of Table 2 for the benefit of the public. For the Examiner's convenience, an additional 'clean' copy of Table 2 is presented in Appendix A.

For at least the above reasons, the Examiner is respectfully requested to withdraw the objection to the amendments to the specification.

Rejection under 35 U.S.C. §112, First Paragraph

Claims 60, 67, 73-78, and 105 were rejected under 35 U.S.C. §112, first paragraph, as being considered to contain matter that was not described in the specification. Applicants respectfully traverse the grounds for this rejection for at least the following reasons.

The Office Action at page 3, item 9, identifies nine phrases (labeled for convenience A through I) as representing "a departure from the specification and the claims as originally filed". Applicants will indicate in the following paragraphs that the specification contains support for each of these phrases.

A. and B. Because the following description of support for the phrases labeled 'A' is similar to that for the phrases labeled 'B', these items will be discussed together.

A. Claim 60 (a): an amino acid sequence extending from amino acid 58 through the C-terminus of SEQ ID NO:4 or 6;

Claim 60 (b): an amino acid sequence extending from amino acid 58 through the C-terminus of SEQ ID NO:13; and

Claim 60 (c): an amino acid sequence extending from amino acid 58 through the C-terminus of SEQ ID NO:15.

B. Claim 67 (a): an amino acid sequence extending from amino acid 58 through the C-terminus of SEQ ID NO:10 or 12;

Claim 67 (b): an amino acid sequence extending from amino acid 58 through the C-terminus of SEQ ID NO:14;

Claim 67 (c): an amino acid sequence extending from amino acid 58 through the C-terminus of SEQ ID NO:16; and

Claim 67 (d): an amino acid sequence extending from amino acid 58 through the C-terminus of SEQ ID NO:31.

The above phrases refer to amino acid sequences of polypeptides from which signal sequence residues have been removed. The signal sequence for the nectin-3 polypeptides is described at page 4 of the specification, line 39 through page 5, line 5 (emphasis added):

The signal sequence for nectin-3 α , β , or γ is located and begins between about amino acid 1 to 39 and extends to about amino acid 57 (e.g., from x_1 to about 57, wherein x_1 is an amino acid between 1 and 39) of SEQ ID Nos: 6, 12, and 31, with the mature polypeptide formed by cleavage following the signal sequence. Typically the signal sequence is cleaved following amino acid 50, 55, or 57, depending upon factors such as the host cell used. Accordingly, the mature polypeptide comprises an amino acid sequence starting at an amino acid between, and including, residue 51 and 58 (e.g., at amino acid 51, 52, 53, 54, 55, 56, 57, or 58;) of SEQ ID Nos: 6, 12, and 31.

The above provides support for mature polypeptides extending from amino acid 58 of SEQ ID NO:6 through its C-terminus, and from amino acid 58 of SEQ ID NO:12 through its C-terminus, and from amino acid 58 of SEQ ID NO:31 through its C-terminus.

SEQ ID NO:4 and SEQ ID NO:6 differ from each other only at amino acid positions 5 and 6 (see page 6, line 38, through page 7, line 4, of the specification, and the Sequence Listing), therefore an amino acid sequence extending from amino acid 58 through the C-terminus of SEQ ID NO:4 is identical to an amino acid sequence extending from amino acid 58 through the C-terminus of SEQ ID NO:6. Similarly, SEQ ID NO:10 and SEQ ID NO:12 differ from each other only at amino acid positions 5 and 6 (see page 6, line 38, through page 7, line 4, of the specification, and the Sequence Listing), therefore an amino acid sequence extending from amino acid 58 through the C-terminus of SEQ ID NO:10 is identical to an amino acid sequence extending from amino acid 58 through the C-terminus of SEQ ID NO:12.

The polypeptides of SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, and SEQ ID NO:16 comprise nectin-3 N-terminal amino acid sequences including nectin-3 signal sequences (page 17, lines 12-17). Polypeptides of SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, and SEQ ID NO:16 from which the signal sequence has been removed are described at page 7, lines 5-6 and also at page 52, line 23 ("The soluble form of the molecule is then predicted to start at amino acid 58 of SEQ ID NO:13 or 14").

The specification therefore provides support for polypeptides having N-terminal nectin-3 amino acid sequences from which the nectin-3 signal sequence has been removed, resulting in such polypeptides having an amino acid sequence extending from amino acid 58 through the C-terminus of the polypeptide. Phrases A and B as used in claims 60 and 67 do not, for at least these reasons, represent new matter.

C. and F. The phrase labeled 'C' is identical to the phrase labeled 'F': "amino acids 58 through 342 of SEQ ID NO:31";

D. and G. The phrase labeled 'D' is identical to the phrase labeled 'G': "amino acids 74 through 342 of SEQ ID NO:31";

E. and I. The phrase labeled 'E' is identical to the phrase labeled 'I': "amino acids 74 through 365 of SEQ ID NO:31";

H. The phrase labeled 'H' is "amino acids 58 through 365 of SEQ ID NO:31".

Because the following description of support applies similarly to the phrases labeled 'C' through 'I', these items will be discussed together.

As described at page 4, lines 38-39 of the specification: "Nectin-3 α , β , and γ are related to each other as the products of alternative splicing: the N-terminal 356 amino acids of the full-length amino acid sequences of these polypeptides are identical." SEQ ID NO:31 is human nectin-3 γ (page 4, lines 33-34 and the Table on page 60 of the specification). Therefore, amino acids 1 through 356 of SEQ ID NO:31 are identical to amino acids 1 through 356 of SEQ ID NOs 6 and 12 (human nectin-3 α and -3 β , respectively). Based on this identity and on the similarity between SEQ ID NOs 4 and 6, and SEQ ID NOs 10 and 12, as discussed above (see page 6, line 38, through page 7, line 4, of the specification), it follows that amino acids 58 through 342 of SEQ ID NO:31 are identical to amino acids 58 through 342 of SEQ ID NOs 4, 6, 10, and 12; and amino acids 74 through 342 of SEQ ID NO:31 are identical to amino acids 74 through 342 of SEQ ID NOs 4, 6, 10, and 12.

As described at page 5, lines 20 through 25 of the specification, nectin-3 β (SEQ ID NO:12), and nectin-3 γ (SEQ ID NO:31) share additional amino acid sequences, having the same extracellular and transmembrane sequences. Therefore, amino acids 58 through 365 of SEQ ID NO:31 are identical to amino acids 58 through 365 of SEQ ID NOs 10 and 12; and amino acids 74 through 365 of SEQ ID NO:31 are identical to amino acids 74 through 365 of SEQ ID NOs 10 and 12.

These similarities among the nectin-3 polypeptides of the disclosure have been previously presented in a graphical form by Applicants; the Examiner is respectfully directed to the following amino acid alignment, which was submitted by Applicants in October 2002 as part of the Response to the Restriction Requirement:

Alignment of SEQ ID NOs 2, 4, 6, 8, 10, 12, and 31:

		1				50
NO2	NEC3ALPHA	~~~~~SPL	CPGGGKAQLS	SASLLGAGLL	LQPPTPPPLL	LLLFPLLLFS
NO4	NEC3ALPHA	MARTpgPSPL	CPGGGKAQLS	SASLLGAGLL	LQPPTPPPLL	LLLFPLLLFS
NO6	NEC3ALPHA	MARTlrPSPL	CPGGGKAQLS	SASLLGAGLL	LQPPTPPPLL	LLLFPLLLFS
NO8	NEC3BETA	~~~~~PSPL	CPGGGKAQLS	SASLLGAGLL	LQPPTPPPLL	LLLFPLLLFS
NO10	NEC3BETA	MARTpgPSPL	CPGGGKAQLS	SASLLGAGLL	LQPPTPPPLL	LLLFPLLLFS
NO12	NEC3BETA	MARTlrPSPL	CPGGGKAQLS	SASLLGAGLL	LQPPTPPPLL	LLLFPLLLFS
NO31	NEC3GAMMA	MARTlrPSPL	CPGGGKAQLS	SASLLGAGLL	LQPPTPPPLL	LLLFPLLLFS
	Consensus	-----SPL	CPGGGKAQLS	SASLLGAGLL	LQPPTPPPLL	LLLFPLLLFS

		51				100
NO2	NEC3ALPHA	RLCGALAGPI	IVEPHVTAVW	GKNVSLKCLI	EVNETITQIS	WEKIHGKSSQ
NO4	NEC3ALPHA	RLCGALAGPI	IVEPHVTAVW	GKNVSLKCLI	EVNETITQIS	WEKIHGKSSQ
NO6	NEC3ALPHA	RLCGALAGPI	IVEPHVTAVW	GKNVSLKCLI	EVNETITQIS	WEKIHGKSSQ
NO8	NEC3BETA	RLCGALAGPI	IVEPHVTAVW	GKNVSLKCLI	EVNETITQIS	WEKIHGKSSQ
NO10	NEC3BETA	RLCGALAGPI	IVEPHVTAVW	GKNVSLKCLI	EVNETITQIS	WEKIHGKSSQ
NO12	NEC3BETA	RLCGALAGPI	IVEPHVTAVW	GKNVSLKCLI	EVNETITQIS	WEKIHGKSSQ
NO31	NEC3GAMMA	RLCGALAGPI	IVEPHVTAVW	GKNVSLKCLI	EVNETITQIS	WEKIHGKSSQ
	Consensus	RLCGALAGPI	IVEPHVTAVW	GKNVSLKCLI	EVNETITQIS	WEKIHGKSSQ

		101				150
NO2	NEC3ALPHA	TVAVHHPQYG	FSVQGEYQGR	VLFKNYSLND	ATITLHNIGF	SDSGKYICKA
NO4	NEC3ALPHA	TVAVHHPQYG	FSVQGEYQGR	VLFKNYSLND	ATITLHNIGF	SDSGKYICKA
NO6	NEC3ALPHA	TVAVHHPQYG	FSVQGEYQGR	VLFKNYSLND	ATITLHNIGF	SDSGKYICKA
NO8	NEC3BETA	TVAVHHPQYG	FSVQGEYQGR	VLFKNYSLND	ATITLHNIGF	SDSGKYICKA
NO10	NEC3BETA	TVAVHHPQYG	FSVQGEYQGR	VLFKNYSLND	ATITLHNIGF	SDSGKYICKA
NO12	NEC3BETA	TVAVHHPQYG	FSVQGEYQGR	VLFKNYSLND	ATITLHNIGF	SDSGKYICKA
NO31	NEC3GAMMA	TVAVHHPQYG	FSVQGEYQGR	VLFKNYSLND	ATITLHNIGF	SDSGKYICKA
	Consensus	TVAVHHPQYG	FSVQGEYQGR	VLFKNYSLND	ATITLHNIGF	SDSGKYICKA

		151				200
NO2	NEC3ALPHA	VTFPLGNAQS	STTVTVLVEP	TVSLIKGPDS	LIDGGNETVA	AICIAATGKP
NO4	NEC3ALPHA	VTFPLGNAQS	STTVTVLVEP	TVSLIKGPDS	LIDGGNETVA	AICIAATGKP
NO6	NEC3ALPHA	VTFPLGNAQS	STTVTVLVEP	TVSLIKGPDS	LIDGGNETVA	AICIAATGKP
NO8	NEC3BETA	VTFPLGNAQS	STTVTVLVEP	TVSLIKGPDS	LIDGGNETVA	AICIAATGKP
NO10	NEC3BETA	VTFPLGNAQS	STTVTVLVEP	TVSLIKGPDS	LIDGGNETVA	AICIAATGKP
NO12	NEC3BETA	VTFPLGNAQS	STTVTVLVEP	TVSLIKGPDS	LIDGGNETVA	AICIAATGKP
NO31	NEC3GAMMA	VTFPLGNAQS	STTVTVLVEP	TVSLIKGPDS	LIDGGNETVA	AICIAATGKP
	Consensus	VTFPLGNAQS	STTVTVLVEP	TVSLIKGPDS	LIDGGNETVA	AICIAATGKP

RCE dated 01 April 2004

Response to Office Action of 03 Oct 2003

		201				250
NO2	NEC3ALPHA	VAHIDWEGDL	GEMESTTTTSF	PNETATIISQ	YKLFPTRFAR	GRRITCVVKH
NO4	NEC3ALPHA	VAHIDWEGDL	GEMESTTTTSF	PNETATIISQ	YKLFPTRFAR	GRRITCVVKH
NO6	NEC3ALPHA	VAHIDWEGDL	GEMESTTTTSF	PNETATIISQ	YKLFPTRFAR	GRRITCVVKH
NO8	NEC3BETA	VAHIDWEGDL	GEMESTTTTSF	PNETATIISQ	YKLFPTRFAR	GRRITCVVKH
NO10	NEC3BETA	VAHIDWEGDL	GEMESTTTTSF	PNETATIISQ	YKLFPTRFAR	GRRITCVVKH
NO12	NEC3BETA	VAHIDWEGDL	GEMESTTTTSF	PNETATIISQ	YKLFPTRFAR	GRRITCVVKH
NO31	NEC3GAMMA	VAHIDWEGDL	GEMESTTTTSF	PNETATIISQ	YKLFPTRFAR	GRRITCVVKH
	Consensus	VAHIDWEGDL	GEMESTTTTSF	PNETATIISQ	YKLFPTRFAR	GRRITCVVKH

		251				300
NO2	NEC3ALPHA	PALEKDIRYS	FILDIQYAPE	VSVTGYDGNW	FVGRKGVNLK	CNADANPPPF
NO4	NEC3ALPHA	PALEKDIRYS	FILDIQYAPE	VSVTGYDGNW	FVGRKGVNLK	CNADANPPPF
NO6	NEC3ALPHA	PALEKDIRYS	FILDIQYAPE	VSVTGYDGNW	FVGRKGVNLK	CNADANPPPF
NO8	NEC3BETA	PALEKDIRYS	FILDIQYAPE	VSVTGYDGNW	FVGRKGVNLK	CNADANPPPF
NO10	NEC3BETA	PALEKDIRYS	FILDIQYAPE	VSVTGYDGNW	FVGRKGVNLK	CNADANPPPF
NO12	NEC3BETA	PALEKDIRYS	FILDIQYAPE	VSVTGYDGNW	FVGRKGVNLK	CNADANPPPF
NO31	NEC3GAMMA	PALEKDIRYS	FILDIQYAPE	VSVTGYDGNW	FVGRKGVNLK	CNADANPPPF
	Consensus	PALEKDIRYS	FILDIQYAPE	VSVTGYDGNW	FVGRKGVNLK	CNADANPPPF

		301				350
NO2	NEC3ALPHA	KSVWSRLDGQ	WPDGLLASDN	TLHFVHPLTF	NYSGVYICKV	TNSLGQRSDQ
NO4	NEC3ALPHA	KSVWSRLDGQ	WPDGLLASDN	TLHFVHPLTF	NYSGVYICKV	TNSLGQRSDQ
NO6	NEC3ALPHA	KSVWSRLDGQ	WPDGLLASDN	TLHFVHPLTF	NYSGVYICKV	TNSLGQRSDQ
NO8	NEC3BETA	KSVWSRLDGQ	WPDGLLASDN	TLHFVHPLTF	NYSGVYICKV	TNSLGQRSDQ
NO10	NEC3BETA	KSVWSRLDGQ	WPDGLLASDN	TLHFVHPLTF	NYSGVYICKV	TNSLGQRSDQ
NO12	NEC3BETA	KSVWSRLDGQ	WPDGLLASDN	TLHFVHPLTF	NYSGVYICKV	TNSLGQRSDQ
NO31	NEC3GAMMA	KSVWSRLDGQ	WPDGLLASDN	TLHFVHPLTF	NYSGVYICKV	TNSLGQRSDQ
	Consensus	KSVWSRLDGQ	WPDGLLASDN	TLHFVHPLTF	NYSGVYICKV	TNSLGQRSDQ

		351				400
NO2	NEC3ALPHA	KVIYISDpPt	ttTlqptiqw	hpStadiedl	atepkklpFp	lstlaTikdd
NO4	NEC3ALPHA	KVIYISDpPt	ttTlqptiqw	hpStadiedl	atepkklpFp	lstlaTikdd
NO6	NEC3ALPHA	KVIYISDpPt	ttTlqptiqw	hpStadiedl	atepkklpFp	lstlaTikdd
NO8	NEC3BETA	KVIYISDVPF	KQT.....	..SSIAVAGA	VIGAVLALFI	IAIFVTVL.L
NO10	NEC3BETA	KVIYISDVPF	KQT.....	..SSIAVAGA	VIGAVLALFI	IAIFVTVL.L
NO12	NEC3BETA	KVIYISDVPF	KQT.....	..SSIAVAGA	VIGAVLALFI	IAIFVTVL.L
NO31	NEC3GAMMA	KVIYISDVPF	KQT.....	..SSIAVAGA	VIGAVLALFI	IAIFVTVL.L
	Consensus	KVIYISD---	-----	-----	-----	-----

		401				450
NO2	NEC3ALPHA	TiatiaaSv	ggalfivlvs	vlagifcyRr	rrtfrgDyF.	..aknYiPps
NO4	NEC3ALPHA	TiatiaaSv	ggalfivlvs	vlagifcyRr	rrtfrgDyF.	..aknYiPps
NO6	NEC3ALPHA	TiatiaaSv	ggalfivlvs	vlagifcyRr	rrtfrgDyF.	..aknYiPps
NO8	NEC3BETA	TPRKKRPSYL	DKVIDLPPTH	KPPPLYEERS	PPLPQKDLFQ	...pEhlPlq
NO10	NEC3BETA	TPRKKRPSYL	DKVIDLPPTH	KPPPLYEERS	PPLPQKDLFQ	...pEhlPlq
NO12	NEC3BETA	TPRKKRPSYL	DKVIDLPPTH	KPPPLYEERS	PPLPQKDLFQ	...pEhlPlq
NO31	NEC3GAMMA	TPRKKRPSYL	DKVIDLPPTH	KPPPLYEERS	PPLPQKDLFQ	vcvhEYt~~~

		451				500
NO2	NEC3ALPHA	dmqKEsqidv	LQqde.LdSy	pdsvkKENkn	pvnnlirkdy	LeepektQwn
NO4	NEC3ALPHA	dmqKEsqidv	LQqde.LdSy	pdsvkKENkn	pvnnlirkdy	LeepektQwn
NO6	NEC3ALPHA	dmqKEsqidv	LQqde.LdSy	pdsvkKENkn	pvnnlirkdy	LeepektQwn
NO8	NEC3BETA	tqfKErevgn	LQhsngLnSr	sfdyedENpv	gedgiqqmvp	LynqmcYQdr
NO10	NEC3BETA	tqfKErevgn	LQhsngLnSr	sfdyedENpv	gedgiqqmvp	LynqmcYQdr
NO12	NEC3BETA	tqfKErevgn	LQhsngLnSr	sfdyedENpv	gedgiqqmvp	LynqmcYQdr

		501				553
NO2	NEC3ALPHA	nvenlnrfer	PmdyYeDlkm	gmkfvsdehy	deneddlvsh	vdgsvisrre wyv
NO4	NEC3ALPHA	nvenlnrfer	PmdyYeDlkm	gmkfvsdehy	deneddlvsh	vdgsvisrre wyv
NO6	NEC3ALPHA	nvenlnrfer	PmdyYeDlkm	gmkfvsdehy	deneddlvsh	vdgsvisrre wyv
NO8	NEC3BETA	spgkhhqnnd	PkrvYiDpre	hyv~~~~~	~~~~~	~~~~~
NO10	NEC3BETA	spgkhhqnnd	PkrvYiDpre	hyv~~~~~	~~~~~	~~~~~
NO12	NEC3BETA	spgkhhqnnd	PkrvYiDpre	hyv~~~~~	~~~~~	~~~~~

Support in the specification for amino acids 58 through 342 and amino acids 74 through 342 of SEQ ID NO:31 can therefore be found in references to amino acids 58 through 342 and amino acids 74 through 342 of SEQ ID NO:6 or SEQ ID NO:12, respectively, because these amino acid sequences are the same (see for example the specification at page 1, line 41 and at page 2, line 2 and lines 7-10). Similarly, support in the specification for amino acids 58 through 365 and amino acids 74 through 365 of SEQ ID NO:31 can be found in references to amino acids 58 through 365 and amino acids 74 through 365 of SEQ ID NO:12 (see for example the specification at page 2, lines 8 and 10). For at least these reasons, there is support in the specification for the phrases C through I as used in claims 73 and 105.

Withdrawal of the rejection of claims 60, 67, 73-78, and 105 under 35 U.S.C. §112, first paragraph, is respectfully requested.

Rejection under 35 U.S.C. §112, First Paragraph

Claims 59-111 were rejected under 35 U.S.C. §112, first paragraph, for allegedly lacking enablement.

The Office Action concedes (at the bottom of page 3 of the Office Action) that the specification is enabling for "a substantially purified polypeptide comprising an amino acid [sequence] of SEQ ID NO:2, 4, 6, 8, 10, 12 and 31, wherein SEQ ID NO:4, 6, 10, 12, and 31 compris[e] amino acids 74-152, 189 to 250 and 287 to 342, and SED ID NO: 13-16, wherein the polypeptide consists of amino acid sequence that binds to nectin-1 for inhibiting endothelial cell migration." Given this statement in the Office Action, Applicants can find no basis for applying this rejection to claims 59-78, such claims being directed to polypeptide sequences that have been shown to possess the nectin-1 binding properties referred to (see, for example, Examples 4 through 6 at pages 53-56 of the specification). Applicants respectfully request that the rejection be withdrawn with respect to claims 59-78, or that the Examiner provide the basis for applying the rejection to these claims.

With respect to claims 79-111, the Office Action states grounds for rejection that appear to fall into two general categories: (1) it would purportedly require undue experimentation to produce the number of variants encompassed by the claims; and (2) the claims are considered to not be enabled due to misplaced concerns about the unpredictability of the art. (3) The Office Action also cites *Colbert v. Lofdahl*, but it is unclear how this case

supports the present enablement rejection. These grounds for rejection will be addressed in turn below.

(1). The Office Action, in the second paragraph on page 5 of the Office Action, notes that a large number of variants would have 80% amino acid identity to amino acid sequences such as amino acids 74 through 152, amino acids 189 through 205, or amino acids 287 through 342 of SEQ ID NOs 4, 6, 10, 12, and 31, and expresses a concern that not all of such variations would be "predictive of inhibiting endothelial cell migration", thus requiring a level of experimentation that is "excessive and undue". However, this concern does not consider the *nature* of the experimentation that would be required in using standard techniques, such as those disclosed in the application, to make and test such variants for function. It is well established that routine experimentation, even if it must be performed on numerous variants, does not constitute experimentation that is so undue that it cannot be carried out by those of skill in the art. See, for example, *Ex parte Mark*, 12 U.S.P.Q.2d (BNA) 1904 (BPAI 1989). For at least these reasons, this basis for the rejection of the claims as lacking enablement is inapposite and may properly be withdrawn.

(2). The Office Action, at page 6, cites the Skolnick and Fetrow, Metzler *et al.*, and Martinez *et al.* references for the proposition that the unpredictability of the art would render the skilled artisan unable to make and use the subject matter of the claims. However, as described above, even in the complete absence of any guidance as to which variants of amino acids 74 through 152, amino acids 189 through 205, or amino acids 287 through 342 of SEQ ID NOs 4, 6, 10, 12, and 31 would be functional, the routine experimentation required to make and test such variants would not be so undue as to cause the claimed subject matter to be beyond the skill of the artisan. And as has been conceded by the Office Action at page 5, paragraph 4, Applicants have provided guidance for the production of functional variants.

Further, the references the Office Action relies upon to support the assertion of unpredictability of the art, when read carefully in their entirety, actually demonstrate the fact that the skilled artisan *can* predict which variants are likely to be functional, especially in situations where guidance can be found from comparisons to related polypeptides. These three references, referred to as "Skolnick and Fetrow", "Metzler", and "Martinez", will be discussed further below.

The purpose of Skolnick and Fetrow, 2000, *Trends in Biotech* 18(1): 34-39 is to consider the assignment of biochemical function to proteins generally, based on amino acid sequence and/or on protein three-dimensional structure. Although the article does point out

some limitations in using either sequence information alone or structural information alone (e.g. Box 2 of the article) to predict protein function, the authors also indicate that in many situations sequence-based approaches are *successful* in predicting function from structure. For example, at page 35, column 1 of the article, in the section entitled "Active-site identification", Skolnick and Fetrow state that the approach of using amino acid sequence conservation as an indication of functionally important residues can be a valid one: "these results provide clear evidence that enzyme active sites are indeed more highly conserved than other parts of the protein". Even in Box 2 of their article, relating to the use of three-dimensional protein structure *alone* to predict function, the authors state that "broad function-structure correlations were observed for some structural classes" of proteins. Also, in the section spanning pages 36 and 37, the authors describe successfully combining sequence and structural information to accurately identify proteins with disulfide-oxidoreductase activity, and they conclude at the bottom of the second column on page 37, "[a]lthough **sequence-based approaches to protein-function prediction have proved to be very useful**, alternatives are needed to assign the biochemical function of the 30-50% of proteins *whose function cannot be assigned by any current method*" (emphasis added). Thus, after a thorough reading of Skolnick and Fetrow, one would more fairly conclude that this reference teaches that sequence-based approaches to protein-function prediction can often, perhaps in most instances, be used *successfully*. It is difficult to apply the teachings of the Skolnick and Fetrow reference directly to the nectin polypeptides of the present application, because Skolnick and Fetrow were assessing prediction of protein function either across all classes of protein structures or to particular types of enzymes, but when read in its entirety this reference certainly *cannot* be considered to teach an inability of the skilled artisan to predict the functionality of nectin-3 polypeptide variants from their amino acid sequence, especially when nectin-3 function (inhibiting endothelial cell migration) has already been experimentally established for polypeptides comprising nectin-3 amino acid sequences.

The Metzler reference (Metzler *et al.*, 1997, *Nature Struct Biol* 4: 527-531) was discussed by Applicants in the June 2003 Response but will be discussed further here, because the Office Action of October 2003 again conclusorily cited Metzler, this time as demonstrating that "a single amino acid substitution or *what appears to be an inconsequential chemical modification* will often dramatically affect the biological activity and characteristic of a protein" (page 6 of the Office Action, emphasis added). Applicants respectfully submit that this statement of the Office Action mischaracterizes the teaching of the Metzler reference, and suggests that Metzler teaches unpredictability of the art, when it in fact teaches the opposite. There is no evidence that single amino acid substitutions, as shown in Table 2

at page 530 of the Metzler reference, would appear to one of skill in the art as "*inconsequential chemical modification[s]*". The Table 2 substitutions of the Metzler reference were made in amino acid residues that are either conserved among CTLA4 species homologues as shown in Figure 2 of Metzler, or are conserved among both CTLA4 and CD28 species homologues. Both CTLA4 and CD28 bind to CD80 and to CD86. Because of the art-recognized relationship between evolutionary amino acid sequence conservation and functional importance (as discussed above in reference to Skolnick and Fetrov), CTLA4 residues conserved among all CTLA4 and CD28 family members would be considered by the skilled artisan to be likely to be related to the CD80 and CD86 binding functions of CTLA4, and substitutions in these amino acids would not be considered as "*inconsequential chemical modification[s]*", but rather as having the potential to affect the activity of the polypeptide. And in fact a careful comparison of Table 2 with Figure 2 of Metzler reveals a clear correlation between the degree to which a residue is conserved in the Figure 2 alignment, and therefore its expected functional importance, and the effect that changing that residue has on the function of the polypeptide, as shown in Table 2. For example, CTLA4 residues E31, R33, E46, and K95 are completely conserved in all the sequences in the Figure 2 alignment, and mutation of these residues abolished or reduced binding of CTLA4 to CD80 and CD86. Once again, a thorough analysis of the Metzler reference shows that *it teaches the ability of the artisan to predict the function of polypeptide variants based on comparisons of amino acid sequences*.

The Office Action discusses a newly cited reference, Martinez *et al.*, 2001, *J Virology* 75(22): 11185-11195 that involves the characterization of the HSV entry activity of human and murine nectin-2 polypeptides. Martinez discloses that the HSV entry activity of human nectin-2 is abolished by the replacement of a particular human nectin-2 amino acid with a mouse amino acid (the M89F mutation). The Office Action mistakenly concludes from the Martinez reference that "it is unpredictable if any functional activity will be shared by two polypeptides having less than 100% identity over the full length of their sequences" (Office Action, page 6). In fact, the Martinez reference teaches the ability of the skilled artisan to predict the functional importance of polypeptide residues based on amino acid sequence comparisons. According to the Martinez reference (page 11185, bottom of column 1 and top of column 2), human and murine nectin-1 have HSV entry activity, and human nectin-2 has entry activity for HSV-2 and certain HSV-1 strains, but murine nectin-2 does *not* have entry activity for HSV strains. Previous studies had shown that the interaction of nectin-1 and human nectin-2 with HSV occurs through the V domain (Martinez, 11186 first column), therefore it was *expected* by the authors that segments of the human nectin-2 V domain would

confer HSV entry activity to mouse nectin-2, and conversely, that replacement of certain residues in the human nectin-2 V domain with residues from murine nectin-2, which has no HSV entry activity, would abolish the human nectin-2 HSV entry activity! Once again, there is a correlation between amino acid sequence conservation and importance for biological activity, as demonstrated by Martinez and Exhibit 1 submitted herewith. Exhibit 1 shows an alignment of the human and murine nectin-1 and nectin-2 amino acid sequences, and indicates the A and B segments of the human nectin-2 V domain that the Martinez authors identified as sufficient to confer the HSV entry activity on murine nectin-2 (page 11188, bottom of column 2, and Figure 3A). Within the A and B segments, there are only two amino acids that are shared by the polypeptides that have HSV entry activity (human and murine nectin-1, and human nectin-2), but *not* by murine nectin-2 that lacks HSV entry activity: the M89 and S92 residues of the human nectin-2 sequence. Thus, these residues would be regarded by the artisan as correlated with HSV entry activity and potentially important for HSV entry activity, and this prediction was confirmed experimentally for the M89 residue (Figure 9 of the Martinez reference). It is clear that, in contrast to the assertions of the Office Action, *the Martinez reference provides evidence of the ability of the skilled artisan to use amino acid sequence information to predict biological function of polypeptide variants.*

Therefore, none of these references cited by the Office Action provide support for the rejection of the claims on the basis that they purportedly lack enablement.

(3). The Office Action, at page 7, also cites *Colbert v. Lofdahl*, 21 USPQ2d, 1068 (BPAI 1992), but it is unclear what relevance this case has to the present rejection of the claims on the basis of an asserted lack of enablement. In *Colbert v. Lofdahl*, the issue was whether physical importation into the United States of bacteria plates containing a clone having protein A activity was sufficient to establish conception of the invention (a recombinant DNA molecule encoding protein A). In the present application, Applicants have provided nectin-3 amino acid sequences, and have provided guidance (as conceded by the Office Action) in how to make and use functional variants of these amino acid sequences. The Examiner is respectfully requested either to withdraw this basis for the rejection, or to explain with particularity how this case supports the rejection of the claims for an asserted lack of enablement.

For at least the above reasons, the rejection of claims 59-111 under 35 U.S.C. §112, first paragraph (enablement), has been traversed, and withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. §112, First Paragraph

Claims 59-111 were rejected under 35 U.S.C. §112, first paragraph, for allegedly not being described in the specification. This rejection is traversed for at least the reasons presented below.

The basis for rejection, as described at page 8 and particularly at the top of page 9 of the Office Action, appears to be directed at variants of the nectin-3 polypeptides of the invention. Applicants can find no clear basis for applying this rejection to claims 59-78, such claims being directed to polypeptide sequences that have been shown to possess the nectin-1 binding properties referred to (see, for example, Examples 4 through 6 at pages 53-56 of the specification). Applicants respectfully request that the rejection be withdrawn with respect to claims 59-78, or that the Examiner provide the basis for applying the rejection to these claims.

The Office Action supports the rejection of the claims with the conclusory statement on page 9, that "there is no described or art-recognized correlation or relationship between the structure of the invention, the nectin-3 extracellular domain, and its inhibition of endothelial cell migration, the feature deemed essential to the instant invention". However, this statement by the Office Action is misplaced because it does not take into account the teaching of the specification concerning nectin structure and function.

The specification teaches how the structures of the nectin-3 extracellular domain are related to binding interactions with other molecules, and how these binding interactions are involved in biological processes such as endothelial cell migration. The specification teaches, for example, that the extracellular domain of nectin-3 polypeptides contains Ig domains, particularly the N-terminal V-type Ig domain, important for its ability to bind other nectins: "The N-terminal Ig domain of nectin-1 and nectin-2 is a V-type Ig domain, while the two C-terminal Ig domains are C2-type domains. The N-terminal Ig domain of this family of molecules has been shown to be required for binding in *trans* to other nectin molecules on adjacent cells in a hetero- or homotypic fashion." (Page 4, lines 6-9.) "[I]nteraction of nectin polypeptides via their extracellular domains is involved in the movement or migration of epithelial and endothelial cells both in normal wound healing and in abnormal conditions such as restenosis." (Page 12, lines 26-28.) "Because the extracellular domain of nectin polypeptides binds to binding partners such as nectins and viral proteins, the extracellular domain, when expressed as a separate fragment from the rest of a nectin polypeptide, or as a soluble polypeptide fused, for example, to an immunoglobulin Fc domain, is expected to

disrupt the binding of nectin polypeptides to their binding partners." (Page 11, lines 27-31.) Therefore, in contrast to the assertion of the Office Action, the specification *does* teach a relationship "between the structure of the invention, the nectin-3 extracellular domain, and its inhibition of endothelial cell migration".

For at least the above reasons, the rejection of claims 59-111 under 35 U.S.C. §112, first paragraph (written description) is without basis; withdrawal of this rejection is respectfully requested.

If a telephone interview would be helpful in advancing the prosecution of this application, Applicants' attorney invites the Examiner to contact her at the number provided below.

Respectfully submitted,



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Appendix A
U.S. Serial No. 09/972,268
Clean Version of Table 2 as of March 2004

Table 2
Conserved Nectin Amino Acids

(Hs=Homo sapiens)
(Mus=Murine)

HUNECTIN2 (SEQ ID NO:22) HUCD155 (SEQ ID NO:25) HUNECTIN1 (SEQ ID NO:20) HUNECTIN3 (SEQ ID NO:6) HUNECTIN4 (SEQ ID NO:24) consensus	~~~~~ ~~~~~ ~~~~~ MARTLRPSPL ~~~~~	~~~~~ ~~~~~ ~~~~~ CPGGGKAQLS ~~~~~	MARAAALLPS ~~~~~ ~~~~~ SASLLGAGLL ~~~~~MPLSLG	RSPPTPLLWP MARAMAAAWP LAGAAGRWWG LQPPTPPPLL AEMWGPEAWL P W LLL LL	LLLLLLL... LLLVALLVLS L...ALGLTA LLLFPLLIFS LLLLLLASFT
HUNECTIN2 HUCD155 HUNECTIN1 HUNECTIN3 HUNECTIN4	51 ..ETGAQDVR WPPPGTGDVV HUNECTIN1 HUNECTIN3 HUNECTIN4	VQVLPEVRGQ VQAPTQVPGF VQVNDSMYGF IIVEPHVTAV LETSDVVTVV PG VQV V G	LG GTVELPCH LGDSVTLP CY IGTDVVLHCS WGKNVSLKCL LGQDAKLPCF LG V LPC	L.LPPVPGLY LQVPNMEVTH FANP.LPSVK I..EV..NET YRGDS..GEQ P	ISLVTWQRPD VSQLTWAR.. ITQVTWQK.S ITQISWEKIH VGQVAWARVD I QVTW R
HUNECTIN2 HUCD155 HUNECTIN1 HUNECTIN3 HUNECTIN4	101 APANHQNVA HGESGSMVA HUNECTIN1 HUNECTIN3 HUNECTIN4	FHPKMGPSFP FHQTQGPSYS YNPSMGVSV HHPQYGFVSQ LHSGYGLHVS Q VA HP G SV	SPKPGSERLS E....SKRLE ..LAPYRERVE ..GEYQGRVL ..PAYEGRVE Y RVE F	FVSAKQSTGQ FVAARLG... FL..... FKNYSLN... QPPPPRNPL F	DTEAELQDAT ...AELRNAS ...RPSFTDGTDATDGS DAT
HUNECTIN2 HUCD155 HUNECTIN1 HUNECTIN3 HUNECTIN4	151 LALHGLTVED LRMFGLRVED HUNECTIN1 HUNECTIN3 HUNECTIN4	EGNYTCEFAT EGNYTCLFVT EGVYICEFAT SGKYICKAVT EGEYECRVST L L ED EG Y C F T	FPKGSVRGMT FPQGSRSVDI FPTGNRESQL FPLGNAQSST FPAGSFQARL FP GS	WLRVIAKPKN WLRVLAKPQN NLTVMKPTN TVTVLVEPTV RLRVLVPPLP LRVLAKP N	QAEAKQVTF. TAEVQKVQL. WIEGTQAVLR SLIKGPD SLI SLNPGP.ALE L
HUNECTIN2 HUCD155 HUNECTIN1 HUNECTIN3 HUNECTIN4	201SQDPTTTGEPVP AKKGQDDKVL DGGNE...TV EGQGL...TL	VALCISKEGR MARCVSTGGR VATCTSANGK AAICIAATGK AASC.TAEGS T A C S A G	PPARISWLSS PPAQITWHS PPSVVSWETR PVAHIDWEGD PAPSVTWDE PPA I W	LDWEAKETQV LGGMPNTSQV LKGEARVPGD LGEM..ESTT VKGT..TSSR L G S	SGTLAGTVTV PGFLSGTVTV SGTPMAPVTV TSFPNETATI SFKHSRSAAV SG TVTV
HUNECTIN2 HUCD155 HUNECTIN1 HUNECTIN3 HUNECTIN4	251 TSRFTLVPSG TSLWILVPSS ISRYRLVPSR ISQYKLFPTR TSEFHLVPSR TS LVPSR	RADGVTVTCK QVDGKNVTCK EAHQQSLACI FARGRRITCV SMNGQPLTCV A G TC	VEH..ESFEE VEH..ESFEK VNYHMDRFKE VKHP..ALEK VSHP..GLLQ V H FE	PALIPVTLVS PQLLTVNLTSLTLNV DIRYSFILD DQRITHILV L V	RYPPEVSISG YYPPEVSISG QYEPEVTIEG QYAPEVSVTG SFLAEASVRG Y PEVSI G
HUNECTIN2 HUCD155 HUNECTIN1 HUNECTIN3 HUNECTIN4	301 Y.DDN.WYLG Y.DNN.WYLG F.DGN.WYLQ Y.DGN.WFVG LEDQNLWHIG Y D N WYLG	RTDATLSCDV QNEATLTCDA RMDVKLTCKA RKGVNLCNA REGAMLKCLS R A L C A	RSNPEPTGYD RSNPEPTGYN DANPPATEYH DANPPPFKSV EGQPPPSYN NPPPT Y	WSTTSGTFPT WSTTMGPLPP WTTLNGSLPK WSRLDGQWPD WTRLDGFLPS WSTL G LP	SAVAQGSQLV FAVAQGAQLL GVEAQNRITLF GLLASDNTLH GVRVDGDTLG G AQG TL

HUNECTIN2 HUCD155 HUNECTIN1 HUNECTIN3 HUNECTIN4	351 IH.AVDSL FN TTFVCTVTNA VGMGRAEQVI FVRETP.... IR.PVDKPIN TTLCNVTNA LGARQAE LTV QVKEGP.... FKGPINYS LA GTYICEATNP IGTRSGQVEV NITEFPYTPS FVHPLTFNYS GVIYCKVTNS LGQRSDQKVI YISDPPTTTT LQPTIQWHPS F.PPLTTEHS GIYVCHVSNE FSSRDSQVTV DVLDPQEDSG KQ..... F P GTYIC VTN G R Q V V E P	400
HUNECTIN2 HUCD155 HUNECTIN1 HUNECTIN3 HUNECTIN4	401RAS P...RDV..G PLVWGAVGGT LLVLLLLLAGGPSE H...SGISRN AIIFLVLG.. ILVFLILLGIPPE HGRRAGPVPT AIIGGVAGSI LLVLIVVGGI TADIEDLATE PKKLPPFLST LATIKDDTIA TIIASVVGGA LFIVLVSVLAVDLV..SAS VVVVGVI AAL LFCLLVVVVV II GV G LLVLLV G	450
HUNECTIN2 HUCD155 HUNECTIN1 HUNECTIN3 HUNECTIN4	451 SLAFILLRVR RR.....RKS .PGGAGGGAS GDGGFYDPA QVLGNGDPVF GIYFYWSKCS REVLWHCHLC .PSSEHHQSC RN~~~~~ VVALRRRRHT FKGDYSTKKH .VYGNVYSKA GIPQHHPMA QNLQYPDDSD GIFCYRRRT FRGDYFAKNY IPPSDMQES QIDVLQDEL D..SYP.DSV LMSRYHRR.. .KAQMTQKY EEELTLTREN SIRRLSHHT DPRSQPEESV Y RR P I P S	500
HUNECTIN2 HUCD155 HUNECTIN1 HUNECTIN3 HUNECTIN4	501 WTPVVPGPME P.DGKDEEEE EEEKA EKGL MLPPPPALED DMESQLDGSLDEKKAGPLG G.SSYEEEE EEEGGGGGER KVGPHPKYD EDAKRPYFTV .KKENKNP.. .VNNLIRKDY LEEPEKTOWN NVENLNRFER PMDYEDLKM GLRAEGHPDS LKDNSSCSVM SEEPEGRSYS TLTTVREIET QT...ELLSP P EE E	550
HUNECTIN2 HUCD155 HUNECTIN1 HUNECTIN3 HUNECTIN4	551 ISRRVYV~ ~~~~~ DEAEARQDGY GDRTLGYQYD PEQLDLAENM VSQNDGSFIS KKEWYV~ GM.KFVSDEH YDENEDDLVS HV...DGSVI SR...REWYV ~~~~~ GSGRAEEEE QDEGIQAMN HFVQENGTLR AKPTGNGIYI NGRGHLV A D	597

Exhibit 1

	1				50
Nec-1 human	MARm.Laga	aarwwgLaLg	LtaffLpavh	sQvVqVn..d	smYGfiGtdV
Nec-1 mouse	MARm.Laga	aarwwgLaLg	LtaffLpgTh	tQvVqVn..d	smYGfiGtdV
Nec-2 human	MARaaaLlps	rspttpLlwp	LllllLleTg	aQdVrVqvlp	evrGqlGgtV
Nec-2 mouse	MARaavLpps	rlsptlpLp	LllllLgeTg	aQdVrVrvlp	evrGrLggtV
Consensus	MAR---L---	-----L-L-	L----L--T-	-Q-V-V----	---G--G--V
			<--A-->	<-B-->	
	51				100
Nec-1 human	vLhCsfanPl	PsvkItQVTW	Qk.stngskQ	NVAiynPsMG	VSvlaPy..r
Nec-1 mouse	vLhCsfanPl	PsvkItQVTW	Qk.asngskQ	NmAiynPtMG	VSvlpPy..e
Nec-2 human	eLpChllpPv	PqlyIslVTW	QrpdapanhQ	NVAafhPkMG	pSfpsPkpgs
Nec-2 mouse	eLpChllpPt	te.rvsQVTW	Qrldgtv...	.VAafhPsfg	Vdfpnsqfsk
Consensus	-L-C-----P-	P---I-QVTW	Q-----Q	NVA---P-MG	VS---P----
				↑	↑
	101				150
Nec-1 human	eRveFlR...psf	tDdTirLsrL	eleDEGvYiC	EFATFPtGnr
Nec-1 mouse	kRveFlR...psf	iDdTirLsGL	eleDEGmYiC	EFATFPtGnr
Nec-2 human	eRlsFvsakq	stqgdteael	qDaTlaLhGL	tvEDEGnYtC	EFATFPkGsv
Nec-2 mouse	dRlsFvRar.	...petnadl	rDaTlafrGL	rveDEGnYtC	EFATFPnGtr
Consensus	-R--F-R---	-----	-D-T--L-GL	--EDEG-Y-C	EFATFP-G-R
	151				200
Nec-1 human	esqlnLtVmA	KPtNwiEgtg	avlrakkqgd	dkVlVatCtS	anGkPPsvvS
Nec-1 mouse	esqlnLtVmA	KPtNwiEgtr	avlrarkqgd	nkVlVatCtS	anGkPPsavS
Nec-2 human	rgmtwLrViA	KPkNgaEaqk	vtf.....sq	dpttVALCiS	keGrPPariS
Nec-2 mouse	rgvtwLrViA	qPeNhaEaqe	vti.....gp	qsVaVaRCvS	tgGrPParit
Consensus	-----L-V-A	KP-N--E---	-----	--V-VA-C-S	--G-PP---S
	201				250
Nec-1 human	WetrLkGEA.	EyQEirnpnG	TVTVISRYrL	VPSreAhqqs	laCiVnyhmd
Nec-1 mouse	WetrLkGEA.	EyQEirnpnG	TVTVISRYrL	VPSreAhrgs	laCiVnyhld
Nec-2 human	WlssLdwEak	EtQvsqtlaG	TVTvtSRftL	VPSgrAdgvt	vtCkVeh...e
Nec-2 mouse	WissLgGEAk	dtQEpgigaG	TVTtiISRYsL	VPvgrAdgvt	vtCrVeh...e
Consensus	W---L-GEA-	E-QE-----G	TVTVISRY-L	VPS--A----	--C-V-----
	251				300
Nec-1 human	rFkE....sl	TLnVqYePEV	tIeGfdGnWY	LqRmDvkLTC	kadanPPaTe
Nec-1 mouse	rFrE....sl	TLnVqYePEV	tIeGfdGnWY	LqRtDvkLTC	kadanPPaTe
Nec-2 human	sFeEpalipv	TLsVrYpPEV	sIsGyDdNWY	LqRtDatLsC	dvrsNPepTg
Nec-2 mouse	sFeEpiIlpv	TLsVrYpPEV	sIsGyDdNWY	LqRseaiLTC	dvrsNPepTd
Consensus	-F-E-----	TL-V-Y-PEV	-I-G-D-NWY	L-R-D--LTC	----NP--T-
	301				350
Nec-1 human	YhWtTlnGsl	PkgveAQnrt	Lffkqpinys	laqTyICEaT	NpiGTrsqqv
Nec-1 mouse	YhWtTlnGsl	PkgveAQnrt	Lffrqpitys	laqTyICEaT	NpiGTrsgqv
Nec-2 human	YdWsttsGtf	PtsavaAQsq	Lviha.vdsl	fntTfvCtvT	NavGmgraeq
Nec-2 mouse	YdWsttsGvf	PasavaAQsq	Llvhs.vdrn	vntTfICTaT	NavGTgraeq
Consensus	Y-W-T--G--	P-----AQ---	L-----	---T-IC-AT	N--GT-----
	351				400
Nec-1 human	evniteEfPyt	psppehgRrA	pvptaIIIG	vagsiLLvli	vvgGIvvalr
Nec-1 mouse	evniteEfPyt	pt.pehgRrA	qmpptaIIIG	vagsvLLvli	vvgGIivalr
Nec-2 human	vifvrEtPra	sp.....Rdv	plvwgavG	tllvLLlaq	qslafillrv
Nec-2 mouse	vilvrEsP..	st.....agA	.atwIIIG	iaaaiiatav	aqtGIllicrq
Consensus	-----E-P--	-----R-A	-----IIIG	-----LL--	---GI-----

	401		450
Nec-1 human	RRRhthfkGdy stkkhvYGng Ys.KAgiPgh hpPmaqlqy Pddsdekka		
Nec-1 mouse	RRRhthfkGdy stkkhvYGng Ys.KAgiPgh hpPmaqlqy Pddsdekka		
Nec-2 human	RRRrkspGga gggasgdGgf YdpKAqvlgn gdPvfwtpvv Pgpme.....		
Nec-2 mouse	gRkeqrlqaa deeeeleG... ..ppsykPpt pkakleepem Psqlf.....		
Consensus	RRR----G-- -----G-- Y--KA--P-- --P----- P-----		
	451		500
Nec-1 human	qPLGgSsyEE EEEEEEGggg GerkvggphP kYdEdakrPy ftvDeaEarg		
Nec-1 mouse	sPLGgSsy.E EEEEEEGggg GerkvggphP kYdEdakrPy ftvDeaEarg		
Nec-2 human	.PdGkd..EE EEEEEekaek GIm.....lP ...p....Pp aleDdmEsqI		
Nec-2 mouse	.tLGaS..Eh spvktpyfda GvscadqemP rYhE....lp tleersgplI		
Consensus	-PLG-S--EE EEEEE----- G-----P -Y-E----P- ---D--E---		
	501		550
Nec-1 human	DGygdrtlgy qydPeqlIda enmvSqnDgs fiskkEwyv~ ~~~~~		
Nec-1 mouse	DGygdrtlgy qydPeqlIda enmvSqnDgs fiskkEwyv~ ~~~~~		
Nec-2 human	DGslisrrav yv~~~~~ ~~~~~ ~~~~~ ~~~~~		
Nec-2 mouse	lGatqlgpsi lvpPgpnvve qvslSleDee eddeeEdfld kinpiydals		
Consensus	DG----- ---P----- ---S--D-- -----E-----		
	551		571
Nec-1 human	~~~~~ ~~~~~ ~		
Nec-1 mouse	~~~~~ ~~~~~ ~		
Nec-2 human	~~~~~ ~~~~~ ~		
Nec-2 mouse	ypspdsyqs kdffvsramy v		
Consensus	-----		